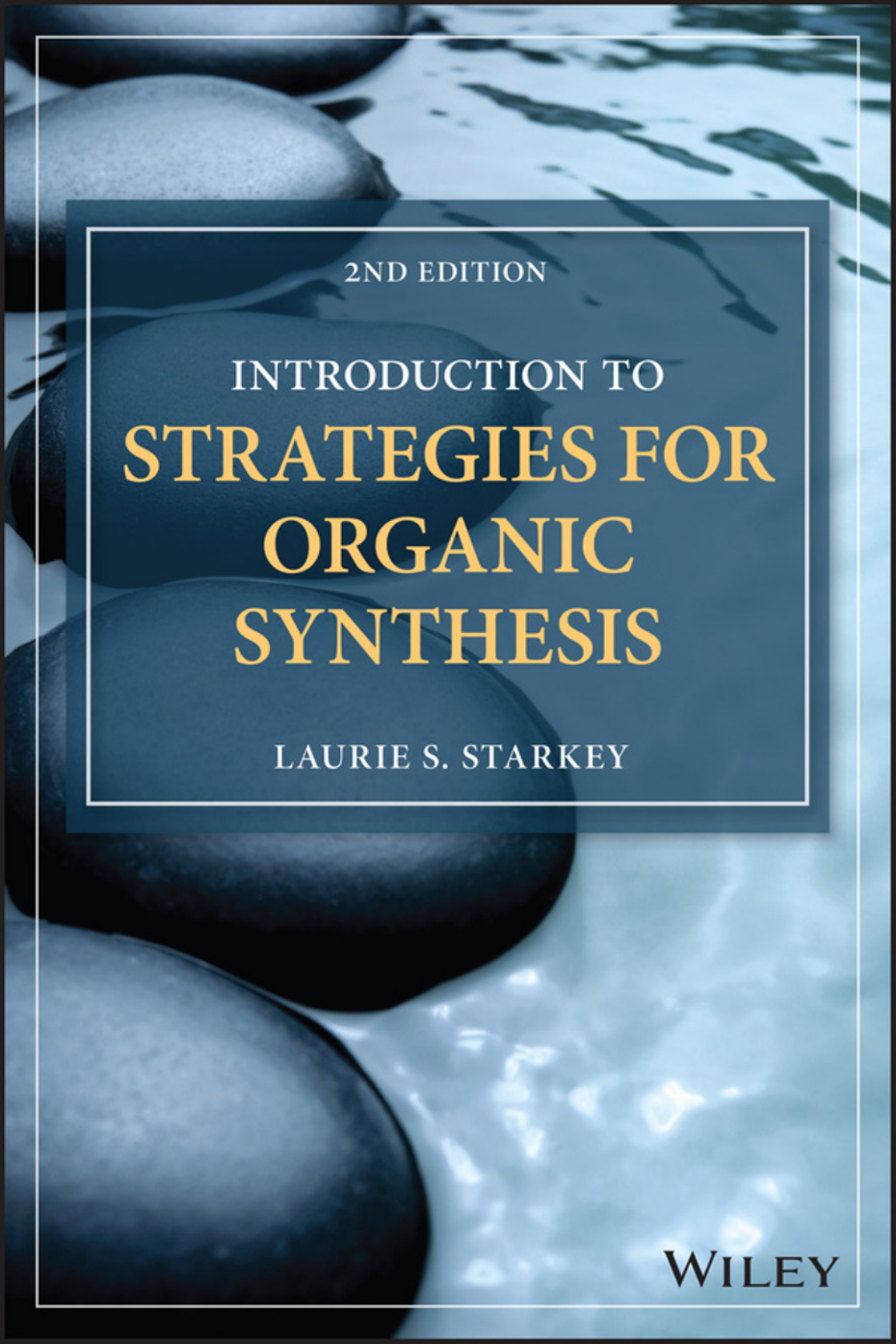
2ND EDITION
INTRODUCTION TO
STRATEGIES FOR ORGANIC SYNTHESIS
LAURIE S. STARKEY
WILEY

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SECOND EDITION

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PREFACE

I really could have used this book when I started graduate school! I became fascinated with organic synthesis ever since running my first Grignard reaction as an undergraduate student at the University of Connecticut. As I watched the magnesium metal disappear into the solvent in my round-bottom flask, I was intrigued by the thought of making new molecules. Although my interest and enthusiasm continued as I entered graduate school at UCLA, I quickly found myself being thrown into the proverbial deep end when I took my first graduate course in organic synthesis. I had never taken a synthesis course at UConn, and my undergraduate organic chemistry course seemed like a foggy memory. I scoured every textbook I could find in an effort to stay afloat, but it was a struggle to work through the advanced material I found there. I benefited immensely from the mentorship and patience of my research advisor, and I eventually earned my Ph.D. in organic chemistry. Although I was able to make progress on my graduate research projects, I didn't truly appreciate the strategies of organic synthesis until I taught the course myself as a faculty member. As I embarked on my teaching career at Cal Poly Pomona, I was eager to share my passion for organic synthesis, but I found that most of my students experienced the same difficulties that I had encountered as a student. The quantum leap from sophomore-level organic chemistry to senior-level organic synthesis is nearly insurmountable for some students. I did my best to bridge this gap with my teaching, but it was a challenge since all of the available textbooks were written at the graduate level (or beyond!). Throughout many years of teaching the organic synthesis course, I gradually developed a teaching strategy that seemed to foster student success. My approach involves a significant amount of review of the sophomore-level material (functional group transformations, reagents, and reaction mechanisms) before changing the perspective and attempting to *plan a synthesis* (functional group analysis and making strategic disconnections: the retrosynthesis of a target molecule). Simply put, taking a year of organic chemistry does not make you an organic chemist, so this review is an essential element for most students. Through practice and experience, envisioning a reaction both in the forward direction and in the reverse direction eventually becomes a routine exercise, but it cannot be assumed to be a trivial matter from the beginning. Such an assumption is made when little to no distinction is made between

undergraduate-level and graduate-level organic synthesis courses, and it can result in a frustrating experience for the student. This book is designed as an intermediate-level introduction to the tools and skills needed to study organic synthesis. It contains worked-through examples and detailed solutions to the end-of-chapter problems, so it is ideal for any student who is interested in pursuing research in the field of organic chemistry, including beginning graduate students. For the second edition, over 130 mid-level, in-chapter problems have been added to provide opportunities for practice and self-assessment. With its thorough review of the reactions of organic chemistry and its Study Guide approach, this book aims to build confidence as it deepens students' knowledge. More challenging topics are also explored, with the goal of raising students to a new skill level and preparing them for advanced coursework. To the students studying organic chemistry, I offer this book along with the same advice that I give to my kids (a quote from Mahatma Gandhi), "Live as if you were to die tomorrow. Learn as if you were to live forever."

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I want to thank my students for making this the greatest job in the world, my graduate advisor, Mike Jung, for providing a supportive environment and for believing in a struggling student, and my mentor, Phil Beauchamp, who is both a passionate teacher and an organic synthesis junkie. The preparation of the manuscripts would be impossible without my tireless reviewers, including Phil Beauchamp, Chantal Stieber, Joe Casalnuovo, Chris Nichols, Phil Lukeman, Richard Johnson, and especially Michael O'Donnell, an avid lifelong student of chemistry who somehow found the first edition of my book before it was even finished! Thanks to my extended family for their love, support, and friendship…and for making me the person that I am today. Most of all, I am grateful to my wolfpack, Mike, Ellie, and Andy, because the most important things in life aren't things.

CHAPTER 1

SYNTHETIC TOOLBOX 1: RETROSYNTHESIS AND PROTECTIVE GROUPS

This book will demonstrate how to synthesize target molecules (TMs) that contain various functional groups (FGs) such as C≡C (alkyne), OH (alcohol or carboxylic acid), and C═O (aldehyde, ketone, and many others). The process of planning a synthesis, called a retrosynthesis, is one of the most critical tools within the "toolbox" needed to solve synthesis problems. The method of retrosynthetic analysis is introduced in this chapter and is used throughout the book. This first chapter will also review the use of protective groups in organic synthesis. The second chapter provides additional useful tools needed by the beginning synthesis student, by reviewing common nucleophiles and electrophiles, as well as some general reagents for oxidation and reduction reactions.

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CHAPTER 1.1

RETROSYNTHETIC ANALYSIS

Every organic synthesis problem actually begins at the end of the story, a target molecule (TM). The goal is to design a reasonable synthesis that affords the TM as the major product. In the interest of saving both time and money, an ideal synthesis will employ readily available starting materials and will be as efficient as possible. The planning of a synthesis involves imagining the possible reactions that could give the desired product; this process is called doing a retrosynthesis or performing a retrosynthetic analysis of a TM. A special arrow is used to denote a retrosynthetic step. The ⇒ arrow leading away from the TM represents the question "What starting materials could I use to make this product?" and points to an answer to that question. The analysis begins by identifying a functional group present on the target molecule and recalling the various reactions that are known to give products containing that functional group (or pattern of FGs). The process is continued by analyzing the functional groups in the proposed starting material and doing another retrosynthetic step, continuing to work backward toward simple, commercially available starting materials. Once the retrosynthetic analysis is complete, then the forward multistep synthesis can be developed, beginning with the proposed starting materials and treating them with the necessary reagents to eventually transform them into the desired TM.

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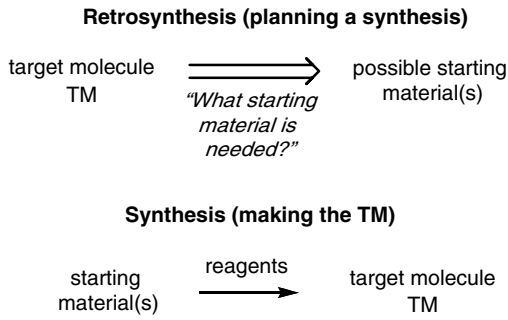


Retrosynthesis and Synthesis of a Target Molecule (TM)

A *retrosynthesis* involves working backward from the given target molecule (work done in our minds and on paper), while the *synthesis* is the forward path leading to the target molecule (experimental work done in the lab). Performing a retrosynthetic analysis is challenging since it requires not only knowledge of an enormous set of known organic reactions but also the ability to imagine the experimental conditions necessary to produce a desired product. This challenge becomes more manageable by developing a systematic approach to synthesis problems.*

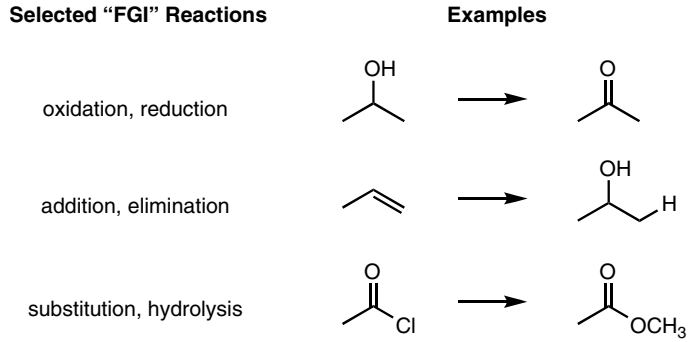
When evaluating a given target molecule, it is important to consider how the functional groups present in the TM can be formed. There are two possibilities for creating a given functional group: by conversion from a different functional group (called a functional group interconversion or FGI), or as a result of a carbon–carbon bond-forming reaction (requiring a retrosynthetic "disconnection"). In order to synthesize a target molecule (or transform a given starting material into a desired product), a combination of FGIs and carbon–carbon bond-forming reactions will typically be required. While the key to the "synthesis" of complex organic molecules is the formation of new carbon–carbon bonds, the synthetic chemist must also be fully capable of swapping one functional group for another.

1.1.1 RETROSYNTHESIS BY FUNCTIONAL GROUP INTERCONVERSION (FGI)

Each functional group has a characteristic reactivity; for example, it might be electron-rich, electron-deficient, acidic, or basic. In order to synthesize organic compounds, we must construct the desired carbon framework while locating the required functional groups in the appropriate

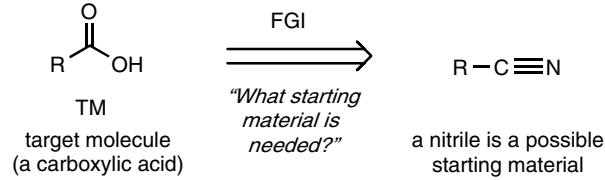
* For the classic textbook on such an approach, see Stuart Warren and Paul Wyatt, *Organic Synthesis: The Disconnection Approach*, 2nd ed. (Wiley, 2009).

positions. This necessitates that the chemist is familiar not only with the reactivities of each functional group but also with the possible interconversions between functional groups. Such functional group interconversions (FGIs) enable the chemist to move along a synthetic pathway toward a desired target.

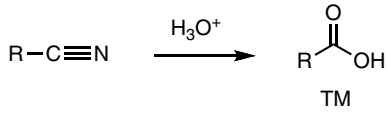


Examples of Functional Group Interconversions (FGI)

Let us consider a carboxylic acid target molecule (RCO_2H). There are many ways to generate a carboxylic acid functional group, so there are many possible syntheses to consider (often, there may be more than one good solution to a given synthesis problem!). One reaction that gives a carboxylic acid product is the hydrolysis of a carboxylic acid derivative, such as a nitrile. Therefore, a possible retrosynthesis of a carboxylic acid TM (What starting materials are needed?) is to consider an FGI and imagine a nitrile starting material. In other words, if we had a nitrile in our hands, we could convert it to a carboxylic acid, leading to a synthesis of the target molecule.



Retrosynthesis of a TM via FGI



Synthesis of the TM

Choice of Reagents

There is almost always more than one reagent that can be used to achieve any given transformation. In fact, a quick look at a book such as *Comprehensive Organic Transformations* by Richard Larock* reveals that there may be dozens of possibilities. Why have so many methods been developed over the years for organic reactions? Because not every molecule—or every chemist—has the same needs. The most obvious reason any "one size fits all" approach fails is that complex synthetic targets contain a wide variety of functional groups. The molecule as a whole must tolerate the reaction conditions used, and side reactions with other functional groups must be kept to a minimum. For example, chromic acid oxidation ($Na_2Cr_2O_7$, H_2SO_4) of a 2° alcohol to give a ketone would not be useful if the starting material contains any functional groups that are sensitive to acidic conditions. In such a case, the Swern oxidation might be preferred (DMSO, ClCOCOCl, Et_3N). New reagents, catalysts, and methods are continuously being developed, with goals of having better selectivity, better tolerance for certain functional groups, being "greener" with less waste or lower toxicity, requiring fewer steps, being more efficient and/or less expensive, and so on.

The focus of this book is on the *strategies* of organic synthesis; it is not intended to be comprehensive in the treatment of modern reagents.† Instead, reagents used are those that are typically found in undergraduate organic chemistry textbooks. Hopefully, these reagents will be familiar to the reader, although they would not necessarily be the ones selected when the synthesis moves from paper to the laboratory. Furthermore, experimental details‡ have largely been omitted from this book. For example, osmium tetroxide oxidation of an alkene is given simply as "OsO_4." In reality, this expensive and toxic reagent is used in catalytic amounts in conjunction with some other oxidizing agent (e.g., NMO), so the precise reagents and experimental reaction conditions are much more complex than what is presented herein.

1.1.2 RETROSYNTHESIS BY MAKING A DISCONNECTION

Rather than being created via an FGI, a functional group (or pattern of FGs) may be created as a result of a reaction that also forms a carbon–carbon sigma bond. In that case, the retrosynthesis involves the disconnection of that

* Richard C. Larock, *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, 2nd ed. (Wiley-VCH, 1999).

† Tse-Lok Ho, *Fieser and Fieser's Reagents for Organic Synthesis Volumes 1–26, and Collective Index for Volumes 1–22, Set*, 1st ed. (Wiley, 2011); Leo A. Paquette et al., *Encyclopedia of Reagents for Organic Synthesis, 14 Volume Set*, 2nd ed. (Wiley, 2009); George Zweifel and Michael Nantz, *Modern Organic Synthesis*, 1st ed. (W. H. Freeman, 2006).

‡ A. I. Vogel et al., *Vogel's Textbook of Practical Organic Chemistry*, 5th ed. (Prentice Hall, 1996).